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Case and Review

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Trauma as Triggering Factor for Development of Melanocytic Nevi

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Key Words
Melanocytic nevus · Trauma · Triggering factor · Eruptive · Predisposition

Abstract
The mechanisms for the development of acquired melanocytic nevi remain mostly unclear. Here we report a case of eruptive nevi that developed after localized superficial trauma, and review the currently known cellular and triggering factors for acquired melanocytic nevi. A 66-year-old woman presented a linear arrangement of pigmented macules on her left calf that developed after a bloodless skin erosion on the same spot, resulting from friction with the lining of a ski boot. Dermatopathology identified multiple junctional proliferations of single or small nest-forming melanocytes with bridging, pigment incontinence and moderate cellular atypia. The number of a person's nevi correlates with age, race and genetics, but blistering diseases, scarring processes, light exposure and immunosuppression can contribute to nevocellular growth as well. Damaged keratinocytes and inflammatory cells can release growth factors inducing nevus cell proliferation, and immunosuppression could end cellular surveillance keeping preexisting nevus cell nests in check. We conclude that in predisposed patients, the trigger for eruptive nevi can be reduced to a simple localized minor trauma.

Case Report

During routine follow-up of a nodular melanoma on the right shoulder, a 66-year-old woman presented a conspicuously linear arrangement of pigmented macules on her left calf. She reported that 2 years earlier, she had suffered from a linear and very superficial bloodless skin erosion at the same spot, resulting from friction with the lining of a ski boot during skiing in the Swiss Alps, which had healed within a few days without leaving any residual structural damage. In the subsequent weeks, however, pigmented macules had developed at the line of the erosion. Her skin type was Fitzpatrick II and she had >50 nevus cell nevi on the whole integument. She did not recall any past intensive sunburn on her legs. Within her family, several members had multiple atypical moles and her brother had developed a melanoma.

Clinical examination (fig. 1a) and dermatoscopy (fig. 1b) of the left calf showed multiple, linearly arranged pigmented macules up to 5 mm in diameter. The lesions had a regular, reticular architecture with symmetry of pattern. In vivo confocal microscopy (fig. 1c, d) revealed pigment in the basal layer of the epidermis and dermal junction. There was no sign of malignancy (no plump bright cells, no dendritic or pagetoid cells within the epidermis). There had been no preexisting lesion in the area where the nevi developed. Dermatopathology (fig. 1e) of one of the macules identified mostly junctional proliferation of single or small nest-forming melanocytes with bridging, pigment incontinence and moderate cellular atypia.

Review of the Literature

Melanocytic nevi are benign proliferations of a type of melanocyte defined as a 'nevus cell' [1]. They are highly prevalent and dynamic lesions. There are 2 subtypes to be differentiated: Congenital melanocytic nevi are present at birth, have lifelong persistence and represent hamartomas probably due to a postzygotic disturbance. Acquired melanocytic nevi instead include all benign melanocytic neoplasia occurring after birth. This group is quite diverse and consistent clinical and histopathological criteria are still lacking [2]. Although their cellular pathogenesis is clear in respect of their development from so-called nevus cells or altered melanocytes, the actual mechanisms causing them to appear or wane again over time mostly remain unclear [3, 4].

Nevus cells and melanocytes are thought to stem from melanoblasts in the neural crest [5], which are formed from specific cells residing at the junction be-

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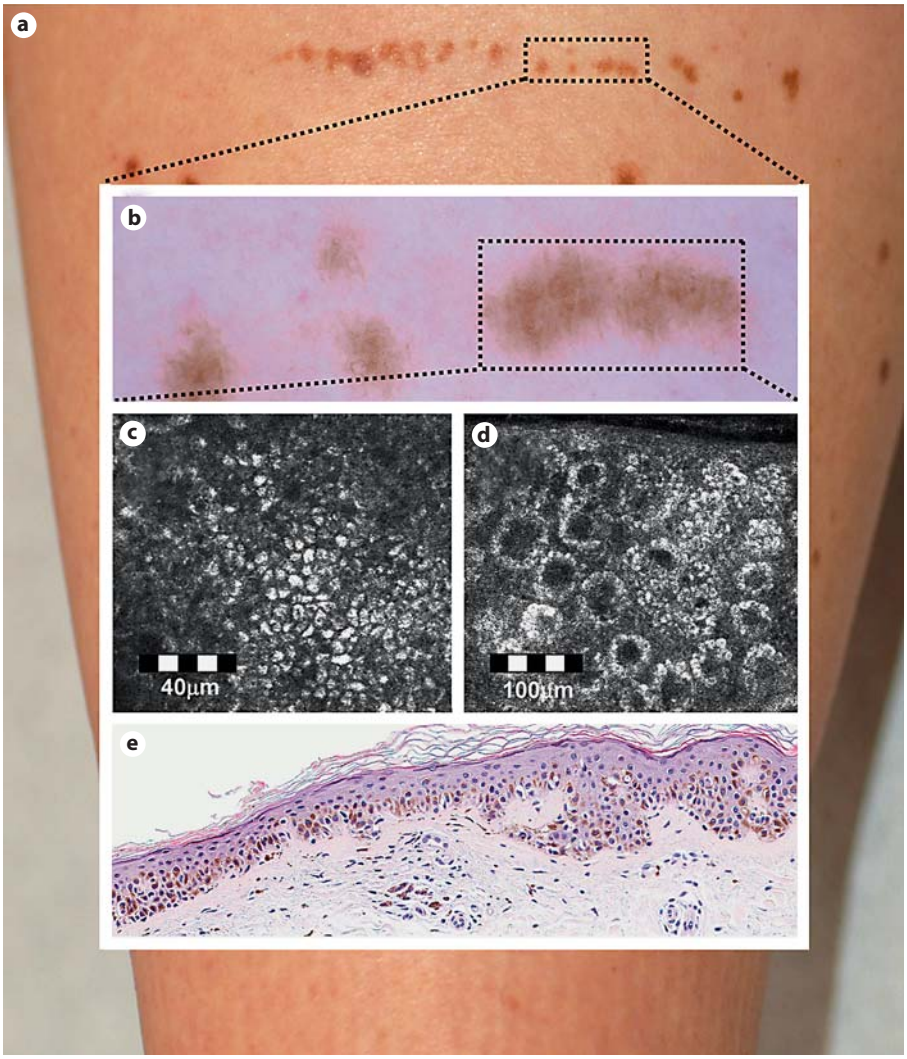

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Fig. 1. a Overview of the left calf of the patient. Dotted line indicates magnified area in **b**. **b** Dermatoscopic view of the linearly arranged pigmented patches shows uniformly fine reticulated pattern. Dotted line indicates area analyzed with confocal microscopy and histology. Magnification ×10. **c** Confocal microscopy capture of the basal cell layer of the lesion. White color reflects supranuclear melanin caps of small round bright keratinocytes, giving a cobblestone appearance. **d** Confocal microscopy capture of the superficial dermoepidermal junction zone shows bright dermal papillary rings composed of a layer of monomorphic bright cells (so-called edged papillae). **e** Hematoxylin-eosin stained biopsy, showing pigmented keratinocytes, isolated nevus cell nests in the upper dermis as well as some pigment incontinence.

tween the surface ectoderm and the neural plate. The signaling proteins Wnt3a and Wnt1 promote the development of neural crest progenitors in pigment cells rather than neuronal cells [6]. Wnt1 promotes expansion of melanoblasts in a paracrine manner. Canonical Wnt signaling then leads to activation of the melanocyte master regulator microphthalmia-associated transcription factor [7] which increases typical melanocyte antigens such as MART1 and GP100 [8].

Melanoblasts are further characterized by high expression of transcription factor SOX10, the tyrosinase kinase receptor KIT, G-coupled receptor EDRNB and melanogenic enzyme DCT [9]. They migrate over considerable distances from the neural crest to the epidermis, starting approximately 1 day later than other neural-crest-derived cells such as cartilage, central nervous system and smooth muscle cell precursors. Although the exact mechanisms responsible for the complicated migration pattern are not understood yet, it appears that cadherins, integrins and extracellular signaling pathways operating through EDRNB are involved [10, 11]. On the way to the target tissues, they start to express tyrosinase, the rate-limiting enzyme for melanin synthesis, and finally take up residence at the dermal-epidermal junction as mature, melanin-positive melanocytes.

How many of these cells represent melanocyte stem cells (MSC) is not clear yet. It is known that there is more than one MSC niche in the skin: the bulge of the hair follicle, the interfollicular epidermis and possibly the sebaceous glands. All these MSC populations have different characteristics, i.e. within the bulge of the hair follicle mostly undifferentiated melanoblasts are found [12]. Several factors (microphthalmia-associated transcription factor, Pax3, SOX10 and DCT) combine to maintain the MSC in a complex interplay. It is not known whether nevus cells and the resulting acquired melanocytic nevi are formed by melanocytes or MSC.

Nevus cells are different from normal melanocytes in 2 ways. They cluster to nests in the lower epidermis or upper dermis, while normal melanocytes are single cells in the basal layer of the epidermis. The second difference is that nevus cells (with the exception of blue nevus cells) do

Table 1. Triggers for the development and/or growth of melanocytic nevi

Light exposure
Sun exposure leading to multiple or severe sunburns
Intermittent intense sun exposure (e.g. on sunny holidays)
Chronic moderate sun exposure (e.g. residence at lower latitudes)
Psoralen and UVA therapy (PUVA)[1]
Neonatal phototherapy
Severe sunburn[1]
Cutaneous injury
Minor trauma (present case)
Köbner phenomenon [50]
Bullous disease
Erythema multiforme[1]
Toxic epidermal necrolysis/Stevens-Johnson syndrome[1]
Epidermolysis bullosa – junctional (particularly generalized atrophic benign) > recessive dystrophic > recessive simplex[1]
Bullae secondary to sulfur mustard gas exposure[1]
Scarring processes
Lichen sclerosus[2]
Systemic immunosuppression
Chemotherapy, particularly for childhood hematologic malignancies[1–3]
Allogeneic bone marrow transplantation[3]
Solid organ transplantation, particularly renal[1, 3]
HIV infection/AIDS[1]
Chronic myelogenous leukemia[1]
Internal malignancy[1]
Anti-tumor necrosis factor therapy (infliximab, etanercept)[1, 3]
Alefacept[1]
Azathioprine[1]
Prednisolone[1]
Methotrexate[1]
6-Mercaptopurine[1]
Increased hormone levels
Pregnancy[1, 4]
Growth hormone (increased size, not number, of nevi)
Addison disease[1]
Thyroid hormone[1]
Other
Atopic dermatitis in children (conflicting results in different studies)
Postoperative fever[1]
Seizures or electroencephalographic abnormalities[1]
Idiopathic[1]

Adapted from Bovenschen et al. [47] and Bolognia et al. [51].

[1] Eruptive nevi have been reported.

[2] An increased number of atypical nevi may also be seen.

[3] Nevi have a predilection for the palms and soles.

[4] Relative immunosuppression may also play a role; an increase in the size or number of nevi has not been clearly demonstrated for pregnant women in general.

not have dendritic processes [13]. These nevus cells can proliferate within the epidermis, producing junctional nevi. Unna's theory of downward migration was put forward in 1893 [14] to explain the evolution of nevi. It holds that increased numbers of melanocytes at the dermoepidermal junction (lentigo simplex and junctional nevus) eventually form nevus nests (compound nevus) and later translocate completely in the dermis as dermal nevi. However, Unna's theory cannot explain several features of nevi such as maturation, infiltration of adnex structures, infiltration in the deep dermis and neuroid differentiation [2]. Therefore, Cramer [15] put forth the theory of upward migration that is more adapted to explain histopathologic features. It states that nevus cells can reside in the dermis and migrate upwards. At the end of the day, however, both theories might be incomplete and probably melanocytes and nevus cells can migrate in both directions and even horizontally [2].

It is not clear whether the clinical definition of nevi as readily visible cellular aggregates encompasses all nevoid proliferations or just the few largest ones that are identified upon examination of the integument. Are the sites of macroscopic nevi the only regions where nevus cells have lodged themselves and proliferated? Apparently, this might not be the case, as a recent work has shown that dermatoscopically, small nests of nevus cells can be present all over the integument in children [16]. If this finding indicates that everyone of us harbors myriads of clinically invisible nevus nests all over the integument, it would mean that not nevus cell migration but triggering factors make the difference whether an acquired nevus develops or not.

Physical and Temporal Factors

The observation of newly forming acquired melanocytic nevi, eruptive or not, in association with specific triggering factors has been made many times (table 1). The identification of such triggering factors contributing to the development of melanocytic nevi is of great interest and has not yet been completed.

It is known that the prevalence of acquired melanocytic nevi correlates with a person's age, race and genetics. A Scottish study showed that in the first decade of life, an average of 2–3 melanocytic nevi can be found on the whole integument. This number rises to 22–33 nevi in the third decade and sinks again to 4–6 nevi in the seventh decade [17]. Whether the reduction in the number reflects a spontaneous involution of nevi, was not addressed in the study. Both the parents' number of nevi and the Fitzpatrick skin type can influence the number of a person's nevi.

However, next to these static factors that are not easily influenced by external factors, blistering [18] or scarring processes [19] as well as light exposure [20, 21] have been shown to contribute to nevus development. How could these various situations induce nevus growth? In all 3, some local cellular damage in keratinocytes and other cells occurs, releasing or triggering induction of growth factors that could act on melanocytes.

It has been shown that damaged keratinocytes can release cytokines such as α-MSH [22] that could influence nevus cells to form larger nests and macroscopically visible nevi. Regarding nevus development after bullous disease, it has been proposed that either melanocytic hyperplasia accompanies keratinocytic proliferation during the healing phase of bullae [23, 24] or that cells of a preexisting nevus residing within the bulla could be spread

within the area of the bulla and set themselves down to form nests, leading to subsequent enlargement of the nevus. In addition, relevant concentrations of interleukin 8 (IL-8), basic fibroblast growth factor, human hepatocyte growth factor, GM-CSF, leukotriene B4 and prostaglandin E2 were identified within bullae, possibly contributing to melanocytic growth [25].

Cellular Factors

Nevus cells depend on several growth factors, among them basic fibroblast growth factor [26]. Binding of the high-affinity receptor FGF-R1 results in cell proliferation [27]. Basic fibroblast growth factor and FGFR-1 are expressed in 55 and 67% of the melanocytic nevi, respectively [28]. Other factors [29] required by melanocytes and nevus cells are insulin, α-MSH and (for cell culture) 12-O-tetradecanoyl-phorbol-13-acetate, which gives the melanocytic cells a selective growth advantage.

Alpha-melanocyte-stimulating hormone (also called α-melanotropin or α-MSH) is derived from pro-opiomelanocortin. It stems from the intermediate lobe of the pituitary gland but can be released ectopically by several cell types including melanocytes. In normal melanocytes, α-MSH can induce melanogenesis and proliferation. Interestingly, it also enhances melanocyte adhesion to fibronectin [30].

Transforming growth factor α and its receptor EGFR have been implicated as important growth factors for melanoma [31, 32]. Normal melanocytes can express transforming growth factor α after UV irradiation [33] – therefore, it could have a role in inducing melanocytic proliferation, i.e. after sunburn [34]. It has been shown to activate the epidermal growth factor receptor and increase proliferation of melanoma but not of normal melanocytes [35].

IL-8 can be produced by melanocytes and melanoma [36]. IL-8-antisense oligonucleotides can inhibit cell proliferation, arguing for the stimulatory role of IL-8 for cell proliferation [36]. Interestingly, IL-6, another proinflammatory cytokine, inhibits melanocyte proliferation [37, 38]. Likewise, proinflammatory TNF-α and -β, IL-1α and -β and oncostatin M can inhibit melanocytic growth.

The MAP kinase pathway has been repeatedly shown to have important roles for melanoma growth. The c-kit receptor bound by its ligand stem cell growth factor activates the microphthalmia transcription factor via the MAP-kinase pathway. This leads to expression of genes that are crucial for melanocyte survival, migration, proliferation, differentiation and pigment production [39, 28]. The c-kit receptor is expressed on the protein level in 70% of the nevi, while stem cell growth factor is expressed in only 23%. Coexpression occurs more commonly in dysplastic nevi [28]. The serine/threonine kinase BRAF (v-raf murine sarcoma viral oncogene homolog B1) is often mutated not only in melanoma but in 86% in melanocytic nevi as well [40]. This indicates that although BRAF probably has a role for proliferative melanoma, it might not be crucial for initial transformation.

Structural and Cellular Interactions

Melanocytes depend on basal membrane contact for survival. In contrast, nevus as well as melanoma cells can survive without constant contact to the basal membrane. Upon exposure to transforming growth factor β1 that they can produce themselves, melanocytes cultured in a collagen gel downregulate the protein Bcl-2, which leads to apoptosis. In contrast, nevus and melanoma cells are resistant to downregulation of Bcl-2 and therefore free to proliferate along 3-dimensional collagen structures [41]. Accordingly, they can be cultured in collagen gels.

A possible step from melanocyte to independent growth could be UVB irradiation. It has been shown that UVB exposure leads to internalization of integrin α6 on melanocytes, loosening their anchorage on the basal membrane [42]. This situation leads to apoptosis in melanocytes. However, with additional mutations such as BRAF the process could be survived and ultimately lead to anchorage-independent nevocellular growth.

Local cellular interactions can influence melanocyte growth and pigmentation. Fibroblasts can inhibit nearby melanocytes by expression of dickkopf1 protein, an inhibitor of the WNT pathway. Thus, palmoplantar fibroblasts expressing dickkopf1 are responsible for reduced melanocytes on our palms and soles, while nonpalmoplantar fibroblasts express dickkopf3, which does not inhibit melanocytes [43].

Systemic Mechanisms for Development of Nevi

Besides local cellular damage due to sunlight, blisters, scarring processes or trauma, systemic immunosuppression [44] as well as hormonal, myelodysplastic [45] and feverish processes have also been observed prior to the development of eruptive nevi. This phenomenon has been explained with constant immunologic factors keeping in check preexisting nevus cell nests [45–48] that proliferate once immunity wanes due to drugs or generalized neoplasia. Blood-borne stimulation of preexisting disseminated nevus nests [16] by cytokines might play an additional role.

A recent report described development of eruptive melanocytic nevi due to immunosuppressive agents including the TNF-α antagonist infliximab and the T cell antagonist alefacept [47], but also more conventional immunosuppressive drugs have been suspected to facilitate the development of nevi (table 1).

In the presented case, linearly arranged dysplastic melanocytic nevi developed after a simple skin erosion due to skiing. In this experiment of nature, the stimulus for the development of these nevi was apparently reduced to a simple small trauma in this likely predisposed patient. Whether these nevi developed by enlarging subclinical nevus nests or whether they were newly formed remains unknown, as is currently the case for all acquired melanocytic nevi. We conclude that in predisposed patients, the trigger for the development of eruptive nevi can be reduced to a simple, localized minor trauma as was first described by Heinrich Köbner [49] for the active phase of inflammatory conditions such as psoriasis.

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